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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 10/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/779,718	BRUNE ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1,8 and 12-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7 and 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/937,296.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix A*.

DETAILED ACTION

Status of the Application

[1] Claims 1-19 are pending in the application.

[2] Applicant's amendment to the claims, filed 19 July 2006, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

Election/Restriction

[3] Applicant's election of Group II, claims 2-7 and 9-11, in the reply filed 19 July 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

[4] Claims 1, 8, and 12-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed 19 July 2006.

Claim to Priority

[5] Applicant's claim to domestic priority under 35 U.S.C. § 120 to US non-provisional application 09/937,296, filed 14 November 2001, now US Patent 6,746,849, is acknowledged. Application 09/937,296 is a filing under 35 U.S.C. § 371 of international application PCT/GB00/01740, filed 5 May 2000. Applicant's claim to foreign priority under 35 U.S.C. § 119(a)-(d) to UK application 9910811.05, filed 10 May

1999, is acknowledged. A certified copy of the foreign priority document was filed 25 September 2001 in parent application 09/937,296.

Information Disclosure Statement

[6] All references cited in the information disclosure statement (IDS) filed 18 February 2004 have been considered by the examiner. A copy of Form PTO-1449 is attached to the instant Office action.

Specification/Informalities

[7] The status of application 09/937,296 should be updated in the priority claim at the first paragraph of the specification. According to USPTO records, application 09/937,296 issued as US Patent 6,746,849.

[8] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: --Method for Detecting the Presence of a Nucleotide Triphosphate in a Sample--.

[9] The listing of references in the specification (p. 14) is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[10] Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites the limitation "the NDPK of *Myxococcus xanthus* carrying a Asp112->Cys mutation." There is insufficient antecedent basis for this limitation in the claim. Also, it is noted that the term "Asp112->Cys" in claim 11 is a relative term which renders the claim indefinite as there is no recitation of a reference sequence of *Myxococcus xanthus* NDPK such that a skilled artisan can determine the position of the mutation as recited in the claim, particularly as the prior art recognizes *M. xanthus* NDPK polypeptides with different amino acid numbering. For example, the *M. xanthus* NDPK as disclosed by the reference of GenBank Accession Number 1NLKL discloses the sequence of a *M. xanthus* NDPK that has a lysine residue at position 112 (see Appendix A). It is suggested that applicants clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[11] Claims 2-7 and 9-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a process for detecting the presence of a nucleoside triphosphate in a sample by detecting the phosphorylation of NDPK to the phosphoenzyme form, optionally wherein the NDPK has been "modified to carry a label which gives a different detectable signal when the enzyme is phosphorylated from when it is unphosphorylated."

The Court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient

to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of NDPK polypeptides, *i.e.,* a Asp112Cys variant of SEQ ID NO:2 with an IDCC label covalently attached to the sulfhydryl of the Cys at position 112. Other than this single species, the specification fails to disclose any other NDPK polypeptides that can be used in accordance with the claimed method and this single disclosed species fails to reflect the wide structural variation among the species of the genus, which encompasses any NDPK polypeptide, having any structure and optionally having any modification that to provide a detectable signal, including any mutants and variants that can be used in accordance with the claimed method. According to MPEP § 2163.II.2.(a).ii), "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In this case, the single disclosed species is insufficient to be representative of the attributes and features of *all* species encompassed by the claims.

Given the lack of description of a representative number of polynucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[12] Claims 2-7 and 9-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for detecting the presence of a nucleoside triphosphate in a sample by detecting a change in the intrinsic fluorescence of an Asp112Cys variant of SEQ ID NO:2 with an IDCC label covalently attached to the sulfhydryl of the Cys at position 112, wherein a decrease in fluorescence of the a Asp112Cys variant of SEQ ID NO:2 with an IDCC label covalently attached to the sulfhydryl of the Cys at position 112 indicates the presence of the nucleoside triphosphate, does not reasonably provide enablement for methods using all NDPKs as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation is required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed

in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: The claims have been interpreted as encompassing the use of any NDPK polypeptide, including mutant and variant polypeptides. In this case, the enablement provided by the specification is not commensurate in scope with the claim, particularly with respect to the broad scope of recited NDPK polypeptides.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: NDPKs that are useful for practicing the claimed method were known at the time of the invention as evidenced by the reference of Deville-Bonne et al. (*Biochemistry* 35:14643-14650, 1996; cited as reference AI in the IDS filed on 18 February 2004) and Schneider et al. (*J Biol Chem* 273:11491-11497, 1998; cited as reference AH in the IDS filed on 18 February 2004). See relevant disclosed teachings of Deville-Bonne et al. and Schneider et al. discussed in detail below. However, as noted above, the claims are not limited to those NDPKs that were known in the art at the time of the invention, and instead encompass numerous mutants and variants of NDPK. The amino acid sequence of a polypeptide determines the its structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid

sequence and obtain the desired activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.*, multiple substitutions. At the time of the invention, methods for isolating or generating variants and mutants of a given polypeptide were known in the art. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for altering all NDPKs with an expectation of obtaining a polypeptide having the desired activity/utility. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity/utility. For example, the reference of Witkowski et al. (*Biochemistry* 38:11643-11650; cited as reference AG in the IDS filed on 18 February 2004) teaches that only a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see *e.g.*, Table 1, page 11647).

The amount of direction provided by the inventor and The existence of working examples: The specification discloses only a single working example of the recited

polypeptide, *i.e.,* an Asp112Cys variant of SEQ ID NO:2 with an IDCC label covalently attached to the sulfhydryl of the Cys at position 112. Other than this single working example, the specification fails to disclose any specific guidance for altering the polypeptide of SEQ ID NO:2 with an expectation that the resulting variants of SEQ ID NO:2 as encompassed by the claims will maintain the desired activity/utility. While it is noted that the specification discloses an Asp62Cys variant of SEQ ID NO:2 (specification at p. 8, middle), there is no evidence of record that this mutant with an IDCC label covalently attached to Cys at position 62 maintains NDPK activity such that the mutant can be used in practicing the claimed method.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating and/or generating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen – by a trial and error process – for all polypeptides having a substantial number of modifications as encompassed by the claims for those that maintain NDPK activity and are useful in accordance with the claimed detection method.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable

correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[13] Claims 2-3 and 9-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Deville-Bonne et al. (*Biochemistry* 35:14643-14650, 1996; cited as reference AI in the IDS filed on 18 February 2004).

The claims are drawn to a process for detecting the presence of a nucleoside triphosphate in a sample by detecting the phosphorylation of NDPK to the phosphoenzyme form.

The reference of Deville-Bonne et al. teaches *Dictyostelium discoideum* NDPK has a single tryptophan residue at position 137 that can be used as a probe for monitoring intrinsic protein fluorescence and that quenching of steady-state fluorescence upon addition of ATP is due to the formation of the phosphorylated

intermediate, *i.e.*, the phosphoenzyme (p. 14643, abstract). Deville-Bonne et al. teaches the addition of ATP to *D. discoideum* NDPK results in a decrease in the fluorescence emission spectra (p. 14647, Figure 3) and quantitatively decreases the mean lifetime of NDPK fluorescence by 19% (p. 14646, right column, middle and p. 14647, Figure 2(a) and Figure 2(b)).

This anticipates claims 2-3 and 9-10 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[14] Claim(s) 4-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deville-Bonne et al. (*supra*) in view of Schneider et al. (*J Biol Chem* 273:11491-11497, 1998; cited as reference AH in the IDS filed on 18 February 2004).

Claim 4 limits the NDPK of the method of claim 2 to being "modified to carry a label which gives a different detectable signal when the enzyme is phosphorylated from when it is unphosphorylated." Claim 5 limits the NDPK of claim 4 to an NDPK that "carries a fluorescent label."

Deville-Bonne et al. discloses the teachings as set forth above. The polypeptide of Deville-Bonne et al. is not modified according to claim 4.

Schneider et al. teaches a mutant *D. discoideum* NDPK that has a Phe at position 64 replaced with Trp and the use of this mutant in measuring binding and affinity constants for NDPK substrates (p. 11495, Table II and Figure 6 and p. 11496, Table III). According to Schneider et al., the mutant stability and steady-state catalytic properties are "similar to those of the wild type enzyme" (p. 11496, right column, bottom) and, due to the presence of the additional Trp residue, intrinsic fluorescence change upon ligand binding is enhanced relative to wild-type NDPK (p. 11495, left column, middle).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Deville-Bonne et al. and Schneider et al. to practice the method of Deville-Bonne et al. for measuring the kinetic constants of *D. discoideum* NDPK using the mutant of Schneider et al. One would have been motivated to do this because of the enhanced fluorescence change upon ligand binding that is observed with the mutant of Schneider et al. as described above. One would have a reasonable expectation of success for practicing the method of Deville-Bonne et al. for measuring the kinetic constants of *D. discoideum* NDPK using the mutant of Schneider et al. because of the results of Deville-Bonne et al. and Schneider et al. Therefore, claims 4-5, drawn to the method as described above, would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

[15] Status of the claims:

Claims 1-19 are pending.

Claims 1, 8, and 12-19 are withdrawn from consideration.

Claims 2-7 and 9-11 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Monday to Thursday, 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

APPENDIX A

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LOCUS       1NLK_L                  144 aa            linear   BCT 04-SEP-1998
DEFINITION  Chain L, Nucleoside Diphosphate Kinase (E.C.2.7.4.6).
ACCESSION   1NLK_L
VERSION     1NLK_L  GI:576202
DBSOURCE    pdb: molecule 1NLK, chain 76, release Mar 1, 1994;
            deposition: Mar 1, 1994;
            class: Phosphotransferase(Po4 As Acceptor);
            source: (Myxococcus Xanthus);
            Exp. method: X-Ray Diffraction.
KEYWORDS    .
SOURCE      Myxococcus xanthus
  ORGANISM  Myxococcus xanthus
            Bacteria; Proteobacteria; Deltaproteobacteria; Myxococcales;
            Cystobacterineae; Myxococcaceae; Myxococcus.
REFERENCE   1  (residues 1 to 144)
  AUTHORS   Williams,R.L., Munoz-Dorado,J., Jacobo-Molina,A., Inouye,S.,
            Inouye,M. and Arnold,E.
  TITLE     Crystallization and preliminary X-ray diffraction analysis of
            oucleoside diphosphate kinase from Myxococcus xanthus
  JOURNAL   J. Mol. Biol. 220 (1), 5-7 (1991)
   PUBMED   1648623
REFERENCE   2  (residues 1 to 144)
  AUTHORS   Williams,R.L., Oren,D.A., Munoz-Dorado,J., Inouye,S., Inouye,M. and
            Arnold,E.
  TITLE     Crystal Structure Of Myxococcus Xanthus Nucleoside Diphosphate
            Kinase And Its Interaction With A Nucleotide Substrate At 2.0
            Angstroms Resolution
  JOURNAL   Unpublished
REFERENCE   3  (residues 1 to 144)
  AUTHORS   Williams,R.L.
  TITLE     Direct Submission
  JOURNAL   Submitted (01-MAR-1994)
COMMENT     Revision History:
            MAY 31 94 Initial Entry.
FEATURES             Location/Qualifiers
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      121 lenakieiay ffreteihsy pyqk
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